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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,752	10/30/2001	Ramy Lidor-Hadas	1662/55002	8981

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EXAMINER	
OH, TAYLOR V	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 11/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/016,752	Applicant(s) LIDOR-HADAS ET AL.	
	Examiner Taylor Victor Oh	Art Unit 1625	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 October 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

   a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *20 October 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *see pages 2-9*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *5-8, 10-22, 25-39, 41, 43, 45-70, and 72-91*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____

13. ☐ Other: _____.

It is noted that applicants have filed an Amendment after the Final Rejection on 10/20/05; applicants' attorney has addressed the issues of record. The proposed amendment will not be entered because it raises a new issue that would require further consideration ; and , it is not in a condition for allowance.

The Status of Claims

Claims 5-8, 10-22, 25-39, 41, 43, 45-70, and 72-91 are pending.

Claims 5-8, 10-22, 25-39, 41, 43, 45-70, and 72-91 have been rejected.

Claim Rejections-35 USC 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of Claims 89-91 under 35 U.S.C. 112, first paragraph, has been maintained due to applicants' failure to modify the claims in the amendment.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of Claims 10 ,16 ,45 and 66 has been maintained due to applicants' failure to modify the claims in the amendment.

Claim Rejections - 35 USC 102

The rejection of Claims 21-22, 49-50, 52, 57-58, 67, 74-76 under 35 U.S.C. 102(b) as being anticipated clearly by Wu Gousheng et al (CN 1113234) has been withdrawn due to applicants' convincing argument. However, the rejection of Claims 19-20, and 66 under 35 U.S.C. 102(b) as being anticipated clearly by Wu Gousheng et al (CN 1113234) has been maintained due to applicants' failure to modify the claims in the amendment. This is because there is no finite description of each of anhydrous ondansetron hydrochloride , anhydrous ondansetron hydrochloride form B and anhydrous ondansetron hydrochloride form E in the claims; therefore, there is no difference among anhydrous ondansetron hydrochloride , anhydrous ondansetron hydrochloride form B and ondansetron hydrochloride form E in comparison with anhydrous ondansetron hydrochloride compounds shown in Wu Gousheng et al (CN 1113234).

Applicants' attorney has addressed the issues of record, but not rebutted the claim rejections ***19-20, and 66*** under 35 USC 102 (b).

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of Claims 5-8, 10-22, and 25-39, 41, 43, 45-70, and 72-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu Gousheng et al (CN 1113234).

The rejection of Claims 5-8, 10-22, and 25-39, 41, 43, 45-70, and 72-91 under 35 U.S.C. 103(a) as being unpatentable over Wu Gousheng et al (CN 1113234) is maintained for the reasons of the record on 7/28/04.

Applicants' attorney has addressed the issues of record, but not rebutted the claim rejections ***5-8, 10-22, 25-39, 41, 43, 45-70, and 72-91*** under 35 USC 103 (a).

The New Issue

The proposed amendment will not be entered because the phrases " to form dihydrate crystals containing about 10 % water " and " collecting the dihydrate crystals by filtration in claim 8 and " the ondansetron hydrochloride that is treated with ketone " in claim 36 which raise a new issue that would require further consideration and search in the processing claims.

Applicants' Argument

I. Applicants argue the following issues:

Applicants' Argument

Applicants argue the following issues:

1. With respect to claims 5-7, the Wu Gousheng reference does not suggest the use of a mixture of ethanol and water ;

2. With respect to claim 8, the Wu Gousheng reference does not suggest hydrating the monohydrate under 50 % relative humidity;

3. With respect to claims 25-38, 39, 41, 43,45, 46-48, 51, 53-56, 59-65, 68-70, and 72-86, the Wu Gousheng reference does not suggest any of these polymorphs , nor any process of preparing them; the Wu Gousheng reference does not suggest the use of particular claimed solvent systems, toluene, xylene, ether, etc. ; therefore, they serve different functionality;

4. With respect to claims 10-18, and 51, the Wu Gousheng reference does not suggest a product having an intermediate degree of hydration nor any process of making such a product;

5. With respect to 19, 62-65, and 72-73, they are related to ondansetron hydrochloride polymorphic forms with different solvents unlike those disclosed in Gousheng;

6. With respect to 39, 41, 43, 87, and 88, they are related to ondansetron hydrochloride polymorphic forms having specific particle sizes unlike those disclosed in Gousheng;

7. With respect to 45, 49-50,52, 57-58, 74-76, and 89-91, they are related to ondansetron hydrochloride polymorphic forms B,C,D,E,H,I, and pharmaceutical compositions ,but Gousheng does not teach any of these polymorphs, any processes for preparing them.

Applicants' arguments have been noted, but the arguments are not persuasive.

First, regarding the first argument , the Examiner has noted applicants' arguments. However, concerning the use of the mixture of ethanol and water , the prior art has offered guidance that the use of water-alcohol solvent is possible in the preparation of Ondansetron hydrochloride (page 2 , lines 29-34). Furthermore, in particularly, Embodiment C_4 (see page 12) does use ethyl alcohol in conjunction with water in the preparation of Ondansetron hydrochloride. The reference is still relevant to the claimed invention.

Second, regarding the second and fourth arguments , the Examiner has noted applicants' arguments. However, concerning the use of the 50 % relative humidity and making an intermediate degree of hydration, the prior art has offered guidance that the final product is rinsed with water in the preparation of Ondansetron hydrochloride (see page 11, Embodiment C); therefore, it possible for the skilled artisan to adjust the exposure of water to the final product depending on the artisan' desirability of increasing water content in the final product. Moreover, the limitation of a process with respect to ranges of pH, time and concentration does not impart patentability to a process when such values are those which would be determined by one of ordinary skill in the art in achieving optimum operation of the process. Concentration is well

understood by those of ordinary skill in the art to be a result-effective variable , especially when attempting to control selectivity of the intended process. The reference is still relevant to the claimed invention.

Third, regarding the third and fifth arguments, the Examiner has noted applicants' arguments. However, concerning the use of making polymorphs and the use of various solvent, it is not uncommon to find several polymorphs of compounds existing under normal handling conditions. The Wu Gousheng reference does teach the use of various solvents, such as benzene and n-propanol, methyl alcohol, and ethyl acetate in the preparation of Ondansetron hydrochloride; therefore, it's quite possible to produce various polymorphs. Furthermore, particular claimed solvent systems such as , toluene, xylene, ether, are well-known solvents in the art, which have a similar functionality as the prior art'solvents. Therefore, there is no patentable weight over the prior art reference in the absence of an unexpected result using the claimed solvent system.

Fourth, regarding the sixth argument , the Examiner has noted applicants' arguments. However, concerning the use of making polymorphs and the use of various solvent, it is not uncommon to find several polymorphs of compounds existing under normal handling conditions. The Wu Gousheng reference does teach the use of various solvents, such as benzene and n-propanol, methyl alcohol, and ethyl acetate in the preparation of Ondansetron hydrochloride; therefore, it's quite possible to produce various polymorphs. Furthermore, particular claimed solvent systems such as , toluene, xylene, ether, are well-known solvents in the art, which have a similar functionality as the prior art' solvents. In addition, regarding the particle size , the limitation of a process

with respect to ranges of pH, time and particle size does not impart patentability to a process when such values are those which would be determined by one of ordinary skill in the art in achieving optimum operation of the process. Particle size is well understood by those of ordinary skill in the art to be a result-effective variable , especially when attempting to control selectivity of the intended process.

Therefore, there is no patentable weight over the prior art reference with respect to the claimed different polymorphic forms having specific particle sizes in the absence of an unexpected result using the claimed solvent system.

Fifth, regarding the seventh argument , the Examiner has noted applicants' arguments. However, with respect to the pharmaceutical composition containing various polymorphic forms, according to the specification, there are some remarks about various polymorphic forms of the Ondansetron hydrochloride, but there are no other information about which polymorphic form in the pharmaceutical composition is effective regarding its bioavailability. It is not uncommon to find several polymorphs of compounds existing under normal handling conditions. Every polymorph has its own characteristic X-ray patterns during the pharmaceutical process of making even the final forms such as tablet or capsule containing the active ingredient. Furthermore, many different polymorphs and /or solvates show varying dissolution rates under different conditions : humidity, pressure, temperature, and etc.. Therefore, on the time scale of the pharmaceutical bioavailability, different total amounts of drug are dissolved, resulting in potential bio-inequivalence of the several forms of the drug. Since the above essential aspects are absent in the specification, the skilled artisan in the art is unable to

determine which one of the polymorphic forms of the Ondansetron hydrochloride is suitable for the pharmaceutical composition with respect to the pharmaceutical bioavailability. Therefore, there is no patentable weight over the prior art reference with respect to the claimed pharmaceutical composition containing different polymorphic forms. Thus, applicants' argument is irrelevant to the issue of the current invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taylor Victor Oh whose telephone number is 571-272-0689. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*** 11/4/05

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